Role of copper in health and diseases

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Abstract

Copper is an essential trace element, playing a critical role in multiple functions in the body. Copper has an important role in maintaining good health. When paired with iron, it helps create red blood cells. It also helps keep blood vessels, bones, nerves, and the immune system healthy. Humans typically ingest copper by drinking water from copper pipes and eating foods like nuts, some fruits and vegetables, shellfish, and red meat. One unique thing about copper is that women need more of it than men. This seems to be primarily because copper is required for the production of the enzymes which convert progesterone into estrogen. This review article presents an up to date findings on the role of copper in every type of conceivable human health and disorders covering a wide variety of common diseases. It is the metal’s deficiency that is manifested in many diseases. The measurement of this metal in additional biological samples like hair, erythrocytes, leucocytes as well as some enzymes like superoxide dismutase, Relative Exchangeable copper and tissue copper will be an useful approach for the differential diagnosis of various diseases pertaining to this metal. As reliable colorimetric method using zinc dibenzyl dithiocarbamate is available and hence measurement of this metal could be carried out in any clinical laboratory. Assayed controls with reference values are readily available with reputed commercial organizations and hence the reliability of results could be easily established. Supplementation studies such as prescribing copper along with iron tablets for better pregnancy outcome could also help the laboratory diagnosis of anemia related gestational problems.

Keywords: copper, zinc, ceruloplasmin, LH, FSH

Received: 10th November; Revised: 28th December 2013; Accepted: 07th January; © IJCS New Liberty Group 2014

Introduction

Copper (Cu) is essential for all living things. As a naturally-occurring element, Cu is present everywhere in the world around us. Life has evolved in this natural presence, and humans have developed built-in mechanisms to manage intake levels. Cu is not manufactured or stored in the body and must be obtained from food and drinking water each day as part of a balanced diet and, occasionally, through the use of dietary supplements. Some foods are especially rich in Cu. These include nuts (especially brazils and cashews), seeds (especially poppy and sunflower), chickpeas, liver and oysters. Natural foods such as cereals, meat and fish generally contain sufficient Cu to provide up to 50% of the required Cu intake in a balanced diet. Virtually every cell in the body utilises Cu and, together with iron and zinc, Cu makes up the trio of micro minerals essential to our well-being. Cu is vital to the health of the body from foetal development right through to old age. Quite simply, without Cu our brains, nervous systems and cardiovascular systems could not function normally. Cu nutrition is especially important for pregnant women, the developing foetus and new-born babies. A
typical recommended daily requirement is 1.2 mg for adults and 0.5-1 mg for children. Cu has been used as a medicine for thousands of years including the treatment of chest wounds and the purifying of drinking water. This review article presents the up to date developments in the role of copper in a wide spectrum of every conceivable human disease highlighting its clinical usefulness.

Copper and Wilson’s diseases

Wilson's disease (WD) is an inherited disorder of copper metabolism leading to liver failure and/or neurological impairment. Its diagnosis often remains difficult even with genetic testing. Relative exchangeable copper (REC) has recently been described as a reliable serum diagnostic marker for WD. REC appears to be independent of demographic or clinical data in Long Evans Cinnamon (LEC) rats. It is a very simple and reliable blood test for the diagnosis of Cu toxicosis owing to a lack of ATP7B gene function. Exchangeable Cu (CuEXC) can be used as an accurate biomarker of Cu overloads (Schmitt et al., 2013). Anti-Cu treatment should prevent clinically overt WD in pre-symptomatic patients but this has not been supported by strong evidence. The use of anti-Cu agents in clinically pre-symptomatic patients diagnosed with WD allows clinically overt disease to be effectively prevented. However, compliance with therapy is extremely important (Dziezye et al., 2013). In WD, Cu accumulates in the liver and extrahepatic organs such as the brain and cornea. Patients may present with combinations of hepatic, neurological and psychiatric symptoms. In the 1930s, the copper-chelating properties of British anti-lewisite and the chemical analysis for Cu of the organs of deceased WD patients have been used from the mid-to-late 1940’s (Purchase, 2013). The long-term outcome of WD patients presenting with acute liver failure (ALF) and those with acute-on-chronic liver failure (ACLF) have not yet been well documented. Patients with WD presenting with acute-on-chronic liver failure manifested symptoms later and had more liver complications than patients with acute liver failure, as well as a lower cumulative free period from liver complication or death (Thanapirom et al., 2013). Rhodanine helps differentiate chronic biliary diseases (CBD) from other conditions, including venous outflow impairment; in the absence of advanced fibrosis, rhodanine positivity strongly favors CBD. In contrast, rhodanine positivity is nonspecific in cirrhosis, but the absence of Cu in that setting excludes CBD (Mounajeed et al., 2013).

Copper and Liver Cancer

Cu accumulation and changes in copper-related gene expression may be contributing factors in liver neoplasia in peroxisome proliferator (PP)-treated rats. Low level of ceruloplasmin (CP) results in decreased free radical scavenger capacity and thus may enhance oxidative damage induced by PPs (Eagon et al., 2013). The spectrum of liver disease includes mild inflammation, fatty liver, an autoimmune disorder, and cirrhosis. WD thus resembles drug hepatotoxicity, and indeed it can be regarded as a prototypic example of endogenous hepatotoxicity. Biomarkers developed for detecting drug hepatotoxicity may be relevant to WD. Biomarkers developed through metalloproteomics for which Cu seeks to define a set of proteins that have Cu-binding capacity, or through genomic studies may also be relevant to WD and other disorders of Cu handling, whether Cu is deficient or overloaded (Roberts et al., 2008). Disulfiram (DSF), a member of the di-thiocarbamate family capable of binding Cu and an inhibitor of aldehyde dehydrogenase, is currently being used clinically for the treatment of alcoholism. Recent studies have suggested that DSF may
have antitumor and chemo-sensitizing activities, although the detailed molecular mechanisms remain unclear. Cu has been shown to be essential for tumor angiogenesis processes. Consistently high serum and tissue levels of Cu have been found in many types of human cancers, including breast, prostate, and brain, supporting the idea that Cu could be used as a potential tumor-specific target. Inhibition of the proteasomal activity can be achieved by targeting tumor cellular Cu with the nontoxic compound DSF, resulting in selective apoptosis induction within tumor cells (Chen et al., 2006).

Copper and alcoholism

The role of trace elements in the pathogenesis of liver cirrhosis and its complications is still not clearly understood. Zinc (Zn), Cu, manganese and magnesium are essential trace elements whose role in liver cirrhosis and its complications is still a matter of research. Scientists agree that the toxic effects of Cu are related to oxidative stress. Manganese is a structural part of arginase, which is an important enzyme in the urea metabolism. Manganese acts as an activator of numerous enzymes in Krebs cycle, particularly in the decarboxylation process (Nova publis). Liver Cu and urinary iron, Zn, and Cu excretion seem to be related with severity of chronic alcoholic liver disease. Low urinary manganese excretion may play a role on liver manganese overload (Rodriguez-Moreno et al., 1997).

Chronic alcoholics frequently show associated malnutrition. Both ethanol and malnutrition exert profound changes on Zn and Cu metabolism. Hair Cu was significantly related to the amount of ethanol consumed, whereas hair Zn was higher in consumers of distilled beverages. No relation was observed between hair Zn and Cu and nutritional status, kind of diet consumed, style of life or liver cirrhosis. Consequently, hair Zn and Cu levels are related only with alcohol intake (Gonzalez-Reimers et al., 2002).

Copper and Reproductive health

A slight, but significant increase in serum Cu levels, not reaching toxic levels, was observed three months after TCu-380A Intrauterine device insertion. Zn levels too had raised significantly, which was quite unexpected, and warrants further investigation (Imani et al., 2013). The entry of Cu and particularly Zn is 1.5-3 times below the physiological norm. Biomonitoring showed high concentrations of lead and cadmium in the body. Regular entry of abiotic metals even in low concentrations in the presence of deficiency of essential metals is fraught with risk of reproductive diseases, which was proven mathematically for all stages of the reproductive function: gestation, labor, and neonatal period (Paran’ko et al., 2002). Decreased levels of serum Cu could be used as a method of choice for detecting infection during the first trimester of pregnancy (Mitreski et al., 2003). Of the nine biological trace elements, Zn, Cu and selenium are important in reproduction in males and females. Cu-deficient female rats are protected against mortality due to Cu deficiency, and the protection has been suggested to be provided by estrogens, since estrogens alter the subcellular distribution of Cu in the liver and increase plasma Cu levels by inducing ceruloplasmin synthesis (Michaluk et al., 2007).

Copper and Hypogonadism

Testosterone deficiency is associated with late-onset hypogonadism. Micronutrients including Cu and Zn influence testosterone synthesis. Subjects with normal testosterone group had a significantly higher Zn level compared to low testosterone group. Significant negative correlations were evident between total testosterone and Cu
level and the Cu/Zn ratio. Normal testosterone is associated with a higher Zn level. Decreased serum testosterone is significantly associated with a high level of Cu and elevated Cu/Zn ratio in hair tissue (Chang et al., 2011). An increase in plasma FSH was demonstrated in groups of both suboptimal Zn and Cu intake. But the plasma LH was elevated only in the group receiving the suboptimal Cu diet, and the added aluminum reversed plasma LH to control levels. A lower level of testosterone was demonstrated in the group given suboptimal Cu with aluminum. It was concluded that dietary aluminum influenced the pituitary-testicular axis by interacting with certain essential trace metals, particularly Zn (Liu et al., 1990).

Copper and thyroid function

Cu plays an important role in thyroid metabolism, especially in hormone production and absorption. Cu stimulates the production of the thyroxine (T4), and prevents over-absorption of T4 in the blood cells by controlling the body calcium levels (Calcium is required for the stabilization of cell membranes and reduces cell permeability). Besides this, Cu is also required for the synthesis of phospholipids, (a class of fats) that are found in the myelin sheaths that insulates nerves to protect them. Phospholipids are required for the stimulation of Thyroid Stimulating Hormone (TSH). Therefore, correct levels are needed to prevent thyroid problems, and can be used in the treatment of thyroid disease (Low Thyroid Advice, 2012). Thiodiazole Cu is likely a thyroid disrupter in female rat following exposure during development, but does not have effect on the development of pubertal female rats. Further studies using environmentally relevant doses are needed for hazard identification (Le Zhang et al., 2009).

Copper and Cardiovascular disease

Although the nutritional essentiality of Cu was established in 1928, a preoccupation with hematology delayed the discovery of cardiovascular disease from Cu deficiency for more than a decade. Anatomical studies of several species of deficient animals revealed, interalia, aortic fissures and rupture, arterial foam cells and smooth muscle migration, cardiac enlargement and rupture, coronary artery thrombosis and myocardial infarction. Cu deficiency also decreases Cu in hearts and other organs and cells and increases cholesterol in plasma. Abnormal physiology from deficiency includes abnormal electrocardiograms and glucose intolerance and hypertension. People with ischemic heart disease have decreased cardiac and leucocyte Cu and decreased activities of some Cu-dependent enzymes. Cu depletion experiments with men and women have revealed abnormalities of lipid metabolism, blood pressure control, and electrocardiograms plus impaired glucose tolerance. The Western diet often is as low in Cu as that proved insufficient for these people. Knowledge of nutritional history can be useful in addressing contemporary nutritional problems (Klevay, 2000). Marginal Cu deficiency, which may affect cardiovascular disease risk, is proposed to occur in many adults in Western industrialized countries. Increased Cu intake raised Cu enzyme activities, but did not consistently improve the cardiovascular health measures studied (Disilvestro et al., 2012). Several prospective studies have found elevated serum Cu concentrations to be associated with cardiovascular disease. Whether Cu directly affects atherogenesis or is a marker of inflammation associated with atherosclerosis remains to be established (Earl Ford, 2000).
Chronic heart failure is a multifactorial syndrome. Several factors had been found to contribute to the development of this syndrome. Low serum Cu level may be one of these contributing factors, probably by elevating blood pressure, impairing different tissue formation and inducing high serum cholesterol level. Measurement of serum Cu level might provide additional and useful laboratory test for the assessment of the patients with chronic heart failure and oral Cu may have a role in therapy (Baybeen et al., 2008). Some nonspecific mechanisms of damage have been implicated in cardiovascular defects of Cu deficiency. They are peroxidation, the interaction of oxygen-derived free radicals with lipids and proteins (possibly DNA); glycation, the non-enzymatic glycosylation of proteins; and nitration, the interaction of nitric oxide and its metabolites with peptides and proteins. Though independently these mechanisms present great potential for damage, the possibility that they may interact presents an added reason for concern. Furthermore, the fact that at least two of these mechanisms are associated with diabetes and aging suggests that Cu deficiency may exacerbate deficits associated with these two conditions (Jack Saari, 2000).

Copper and Kidney function

Ceruloplasmin-related indexes in kidney dialysis patients not dialyzed with Cu-based membranes suggested a tendency toward moderate Cu deficiency. However, this contention could not be confirmed by erythrocyte SOD activity or mononuclear cell Cu measurements (Emenaker et al., 1996). Plasma Cu was higher in the Diabetes Mellitus (DM) group when compared to the Non-DM control groups. Serum urea was a positive independent determinant of plasma Zn concentration. These findings demonstrate an alteration in the distribution of Zn of patients with chronic kidney disease (CKD) independently of the presence of DM. Also, the status of Cu seems not to be influenced by CKD, but only by the metabolic derangements associated with diabetes (Maria Nazare Batista et al., 2006).

Copper and Anemia: Cu deficiency results in the inhibition of differentiation and self-renewal of CD34(+) hematopoietic progenitor cells. A number of recent studies have reported on the association of Cu deficiency with the development of concomitant neurologic deficits manifested as peripheral neuropathies and myeloneuropathy indistinguishable from the findings seen in vitamin B12 deficiency. Patients presenting with refractory anemia and leukopenia with or without associated neurologic deficits should have Cu and CP levels measured as part of their diagnostic evaluation (Lazarchick, 2012). Cu deficiency is rarely reported as a cause of neutropenia and anemia through mechanisms not clearly understood. Two cases of an unexplained Cu deficiency anemia and neutropenia in otherwise healthy young adults found at a single institution over a short period of time suggests that this problem may be more widespread than is currently realized (William Harless et al., 2006). Cu deficiency is an etiology of anemia, neutropenia, and bone marrow dysplasia that may be under-recognized. Cu level assessment in patients with gastrointestinal disorders and neuropathy showed that number of progenitor cells (colony-forming unit-granulocyte-macrophage and erythrocyte) present before the Cu supplementation was well preserved. It is therefore suggested that Cu enzymes play an important role in the maturation of hematopoietic cells (Hirase et al., 1992; Thomas et al., 2007).

Copper and Thalasemia: Hypozincemia is common in thalassemic patients, but in contrast, there is no Cu
deficiency. Further evaluation in this regard is recommended (Mahyar et al., 1992). High level of Cu could be explained by the increase in Cu absorption via the gastrointestinal tract (Kamal Mansi et al., 2010). There is no consensus about Zn and Cu deficiency in patients with thalassemia major. Thalassemic patients had significantly lower Zn and Cu concentration compared with healthy subjects (p < 0.001). The prevalence of low serum levels of Zn and Cu in thalassemic patients was almost two times higher than healthy subjects for Zn and Cu and hence high prevalence of low levels of serum Zn and Cu concentrations was observed in thalassemic patients (Banihashem et al., 2013).

**Copper and Ovarian Cancer**

Serum Cu and Cu/Zn ratio were significantly higher in ovarian cancer patients when compared to patients with benign ovarian lesions. It seems that determination of serum Cu and Cu/Zn ratio may be used as a test for diagnosing of ovarian cancer (Mehri Jafari Shobeiri et al., 2011). CTR2 contributes to platinum resistance in ovarian cancer. The CTR2/CTR1 ratio is a useful marker for platinum sensitivity and a potential prognostic factor in patients with ovarian cancer (Yoshida et al., 2013). The estimation of antioxidants like ceruloplasmin and TBARS along with the trace element like Cu may be of value in the early diagnosis of cancer (Nayak et al., 2004). A possible clinical usefulness of estimating serum Cu levels in women with genital tract cancer and suggest a role for serum Cu in the evaluation of the disease activity and as a prognostic tool in the management of genital malignancies (Saxena et al., 2002).

Alteration in the concentration of Cu and Zn in serum of patients with breast cancer, which may indicate abnormal Cu and Zn metabolism in Nigerian females with breast cancer (Byrne et al., 2013). Free radicals play an important role in colorectal carcinogenesis, while the findings regarding vitamin E are so far unexplained (Polgari et al., 2011). Trace elements and free radicals have been implicated in the etiology of cancer. Hence, determination of specific antioxidants (like ceruloplasmin) and trace elements like Cu may be of value in the early diagnosis of prostate and colon cancer (Nayak et al., 2003). Elevated levels of Cu have been found in many types of human cancers, including prostate, breast, colon, lung, and brain. On this basis, the employment of Cu chelators has been reported to be of therapeutic value in the treatment of several types of cancers as anti-angiogenic molecules. More recently, mixtures of Cu chelators with Cu salts have been found to act as efficient proteasome inhibitors and apoptosis inducers, specifically in cancer cells. Moreover, following the worldwide success of platinum (II) compounds in cancer chemotherapy, several families of individual Cu complexes have been studied as potential antitumor agents. These investigations, revealing the occurrence of mechanisms of action quite different from platinum drugs, head towards the development of new anticancer metallodrugs with improved specificity and decreased toxic side effects (Adaramoye et al., 2010).

**Copper and Mental Retardation**

Cu content and iron content of hair samples from mentally retarded children were significantly lower than those of healthy children (Tian et al., 1998). Malabsorption of Zn and iron were associated with some types of pica although the individuals received adequate dietary intake of minerals. Zn, Cu, and magnesium concentrations in hair were within normal ranges. Hair was a less sensitive indicator than plasma of trace element status (Bruhl et al., 1987).
Copper and Alzheimer's disease

Cu homeostasis is profoundly affected in Alzheimer's Diseases (AD), and accumulated extracellular Cu drives Amyloid β aggregation, while intracellular Cu deficiency limits bioavailable Cu required for CNS functions. Inflammatory events that occur in AD in response to Amyloid β and highlights recent advances on the role of Cu in modulation of beneficial and detrimental inflammatory responses in AD (Choo et al., 2013). The important role that low molecular mass fractions of iron, Cu, aluminium and cobalt appear to play in pathogenesis of AD. Correlation analysis indicated that these metal abnormalities can be interrelated, participating in common processes such as oxidative stress, altered homeostasis and uptake into brain, as well as impaired glucose metabolism (Gonalez-Dominguez et al., 2013). The role of transition metals, in particular Cu, in AD has become significant interest due to the dyshomeostasis of these essential elements, which can impart profound effects on cell viability and neuronal function. There is a brain specific alteration in Cu levels in AD localized to the soluble extracted material, which is not reflected in erythrocytes. Further studies using metalloproteomics approaches will be able to elucidate the metabolic mechanism(s) that results in the decreased brain Cu levels during the progression of AD (Rembach et al., 2013).

Zn therapy significantly lowered blood free Cu levels. So Zn efficacy could be due to restoring neuronal Zn levels, to lowering blood free Cu levels, or to both (Brewer et al., 2013). All the Cu indices analyzed were significantly higher in AD subjects compared to healthy controls (Squitti et al., 2014). Serum Cu levels were significantly negatively correlated with scores on cognitive test subscores. AD patients may have significantly more ‘defective’ ceruloplasmin that is, apo-ceruloplasmin lacking its Cu, than in healthy controls (Park et al., 2013).

Tau, the core protein component of NFTs, is sensitive to interactions with Cu and cholesterol, which trigger a cascade of hyperphosphorylation and aggregation preceding the generation of NFTs (Hung et al., 2013).

Copper and Parkinson disease

Regions affected by α-synuclein pathology may display enhanced vulnerability and cell loss if Cu-dependent protective mechanisms are compromised. Additional investigation of Cu pathology in Parkinson Disease (PD) may identify novel targets for the development of protective therapies for this disorder (Davies et al., 2013). A disturbance of the plasmatic rate of Cu could be a marker of PD or at least, a risk factor for the development of this disease. Although Zn participates in the reduction of oxidative stress and the antioxidant role of the selenium, their implication in the onset of PD is not clearly established and perspectives for the future could include antioxidant therapy. For this reason, other prospective studies should be conducted on this subject to elucidate the implication of trace elements in PD (Younes-Mhenni et al., 2013). Total Cu is significantly lowered in AD brains. This may result in defective synthesis of CP and other Cu enzymes. The defective CP activity, associated with iron disorders, is seemingly of importance in PD and also in AD with other Cu enzyme defects possibly involved (Johannesson et al., 2012). The metaregression for sex revealed that serum Cu differences found in some studies could be referred to the different percentage of women in the PD sample. Transferrin and transferrin saturation levels found increased in PD subjects underline the concept to extend the iron study in PD to iron master proteins (Mariani et al., 2013). The level of Cu
remained unchanged in both on and on/off PD patients. Iron and selenium increase in CSF of both patients which is a clear evidence of relationship between increased iron and selenium level in brain which could be correlated with decrease in dopamine levels and oxidative stress in PD Patients (Qureshi et al., 2006).

**Copper and Obesity**

In obese patients Zn concentrations were significantly lower than in the lean control subjects and Cu levels were significantly higher. Intestinal bypass surgery may produce clinically significant decreases in plasma concentrations of Zn and Cu. Careful observation and replacement therapy are indicated in all patients who develop deficiencies after intestinal bypass surgery (Forte et al., 2005). The obesity associated to disorders in lipid metabolism predisposes to changes in Cu plasma concentrations, but there was no alteration in intracellular reserves, which suggests an important homeostatic control to compensate for plasma oscillations and metabolic alterations of the disease (Omar et al., 2001).

**Copper and Diabetes Mellitus**

In Iron and Cu overloading conditions, Iron and Cu chelating drugs could be used to control diabetes and diabetic complications. The essentiality, toxicity and roles of these metals in the pathogenesis of diabetes and diabetic complications (Lima et al., 2006). Diabetes-evoked Cu dysregulation is an important new target for therapeutic intervention to prevent/reverse organ damage in diabetes, heart failure, and neurodegenerative diseases, and that tri-ethyl-enetetramine (TETA) is the first in a new class of anti-diabetic molecules, which function by targeting these Cu-mediated pathogenic mechanisms. TETA prevents tissue damage and causes organ regeneration by acting as a highly-selective Cu chelator which suppresses Cu-mediated oxidative stress and restores anti-oxidant defenses (Sanchez et al., 2010). Magnesium and Zn administration along with Cu could benefit in type 2 diabetes mellitus and Cu chelators could represent also a future medication in diabetes (Coopr et al., 2012). Zn and magnesium levels are not altered in diabetes mellitus, but the increased Cu levels found in diabetics may merit further investigation of the relationship between Cu and non-insulin dependent diabetes mellitus (Monica Daniela Dosa et al, 2013). Hyperzincnuria and hypermagnesuria were evident in diabetic subjects compared with control subjects. Diabetes can alter Cu, Zn, magnesium, and lipid peroxidation status. Perturbations in mineral metabolism are more pronounced in diabetic populations with specific complications. It is not known whether differences in trace element status are a consequence of diabetes, or alternatively, whether they contribute to the expression of the disease (Zargar et al., 1998).

**Copper and Thymus**

Chronic Cu deficiency in mice impairs both humoral and cell-mediated immunity, but the mechanisms are unknown. Electron micrographs taken of thymus and spleen from Cu-deficient mice demonstrate altered morphology characterized by abnormal mitochondria and misshapen nuclei. Chronic Cu deficiency alters the size, biochemistry and morphology of primary (thymus) and secondary (spleen) lymphoid tissue (Lamber Academic Publish, 2013).

**Copper and Pineal gland**

There was a statistically significant decrease in the N-acetyl serotonin level in the pineals from the 6-week Cu-treated animals, as compared to the control and Cu/melatonin-treated group (p < 0.01). These results imply that Cu reduces N-acetyl-transferase activity, which results

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in a decrease in N-acetyl serotonin synthesis. Melatonin when co-administered with Cu appears to prevent the N-acetyl-transferase inhibition by Cu. Cu exerts contradictory effects on 5-methoxytryptophol synthesis. Further investigations need to be carried out to examine the effects of Cu on the pineal enzymes (Mitra et al., 2013).

Copper and Diarrhea

In a double-blind randomized controlled clinical trial of 724 children aged 6-59 months, none of the 11 evaluated outcomes showed significant association with Zn or Zn and Cu supplementation. Thus, therapeutic Zn supplementation may not always yield short-term benefits (Parmar et al., 2001). Children suffering from acute diarrhea show a statistically significant decrease of 13.1% and 12.8% in serum Zn and Cu concentrations, respectively, compared to normal. These levels further decrease by 22.6% and 22.4%, respectively, after treatment with standard ORS therapy. Children with the lower plasma Zn and Cu levels suffered with more severe and longer duration of diarrhea. Zn and Cu supplementation could be added to standard ORS therapy for the reduction in morbidity and mortality associated with acute diarrhea in children (Patel et al., 2013). Studies assessing the interactions between diarrheal diseases, HIV/AIDS and micronutrient status are too few in Ethiopia, as in other sub-Saharan Africa where morbidities from diarrheal diseases and HIV/AIDS are serious health problems (Arora et al., 2006).

Copper and neonatal disorders

Cu level in all groups of premature infants is lower than in full term infants. This is expected because serum Cu reaches a maximum at the end of last trimester of pregnancy, whereas the livers of premature infants are immature and cannot accumulates the metal. Serum Cu was increased two fold in the neonates with moderate hemolytic jaundice and almost threefold in premature and full-term infants with severe hemolytic jaundice. Measuring serum Cu could provide an additional useful marker for the differential diagnosis between moderate or severe hemolytic and non-hemolytic neonatal jaundice and identify high-risk premature infants. The potential value of chelating agents for the treatment of patients with severe hemolytic jaundice and high Cu could not be assessed, but many countries have limited use of chelation therapy to late childhood and adulthood. α-Tocopherol or other antioxidants may be administrated as usual (Amare et al., 2011). Monitoring Cu ideally requires a liver biopsy but there are reports that in infant’s serum Cu levels correlate with the liver Cu. The published cautions about Cu in cholestatic patients on parenteral nutrition led to the removal of Cu from the solutions. The liver excretion of Cu is the primary regulating method but clinically cholestasis does not result in elevated levels in infants. The best clinical approach to parenteral nutrition Cu is careful monitoring even in the presence of cholestasis (Kleopatra et al., 2004). Cholestasis does not appear to impair Cu excretion enough to result in elevated levels. In fact, infants with gastrointestinal disorders may require higher than standard dosing. Monitoring Cu levels appears to be necessary to appropriately regulate Cu dosing for cholestatic infants receiving parenteral nutrition (Corkins et al., 2011). The essential requirements for Cu in early development in dramatically illustrated by Menkes Disease, a fatal neurodegrative disorder of early childhood caused by loss of function mutation in the gene encoding Cu transporting ATPase (Yanfang Wang et al., 2012).

Conclusion: This review article presents an up to date findings on the role of Cu in every type of conceivable...
human health and disorders covering a wide variety of common diseases. It is the metal’s deficiency that is manifested in many diseases. The measurement of this metal in additional biological samples like hair, erythrocytes, leucocytes as well as some enzymes like SOD, REC and tissue Cu will be an useful approach for the differential diagnosis of various diseases pertaining to this metal. As reliable colorimetric method using Zinc Dibenzyl dithiocarbamate is available, Cu in all types of biological samples could be easily measured. Assayed controls with reference values are available with reputed commercial organizations, the reliability of results could be easily established. Supplementation studies such as prescribing Cu along with iron tablets for better pregnancy outcome could also help the laboratory diagnosis of anemia related gestational problems.

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